Malignant Transformation of CD4⁺ T Lymphocytes Mediated by Oncogenic Kinase NPM/ALK Recapitulates IL-2–Induced Cell Signaling and Gene Expression Reprogramming

Michal Marzec, Krzysztof Halasa, Xiaobin Liu, Hong Y. Wang, Mangeng Cheng, Donald Baldwin, John W. Tobias, Stephen J. Schuster, Anders Woetmann, Qian Zhang, Suzanne D. Turner, Niels Ødum and Mariusz A. Wasik

*J Immunol* published online 11 November 2013
http://www.jimmunol.org/content/early/2013/11/08/jimmunol.1300744
Malignant Transformation of CD4+ T Lymphocytes Mediated by Oncogenic Kinase NPM/ALK Recapitulates IL-2–Induced Cell Signaling and Gene Expression Reprogramming

Michal Marzec,* Krzysztof Halasa,* Xiaobin Liu,* Hong Y. Wang,* Mangeng Cheng,† Donald Baldwin,*‡ John W. Tobias,‡ Stephen J. Schuster,§ Anders Woetmann,¶ Qian Zhang,* Suzanne D. Turner,‖ Niels Ødum,§ and Mariusz A. Wasik*§

Anaplastic lymphoma kinase (ALK), physiologically expressed only by nervous system cells, displays a remarkable capacity to transform CD4+ T lymphocytes and other types of nonneural cells. In this study, we report that activity of nucleophosmin (NPM)/ALK chimeric protein, the dominant form of ALK expressed in T cell lymphomas (TCLs), closely resembles cell activation induced by IL-2, the key cytokine supporting growth and survival of normal CD4+ T lymphocytes. Direct comparison of gene expression by ALK+ TCL cells treated with an ALK inhibitor and IL-2–dependent ALK− TCL cells stimulated with the cytokine revealed a very similar, albeit inverse, gene-regulation pattern. Depending on the analysis method, up to 67% of the affected genes were modulated in common by NPM/ALK and IL-2. Based on the gene expression patterns, Jak/STAT- and IL-2–signaling pathways topped the list of pathways identified as affected by both IL-2 and NPM/ALK. The expression dependence on NPM/ALK and IL-2 of the five selected genes—CD25 (IL-2Rα) chain, Egr-1, Fosl-1, SOCS3, and Irf-4—was confirmed at the protein level. In both ALK+ TCL and IL-2–stimulated ALK− TCL cells, CD25, SOCS3, and Irf-4 genes were activated predominantly by the STAT5 and STAT3 transcription factors, whereas transcription of Egr-1 and Fosl-1 was induced by the MEK-ERK pathway. Finally, we found that Egr-1, a protein not associated previously with either IL-2 or ALK, contributes to cell proliferation. These findings indicate that NPM/ALK transforms the target CD4+ T lymphocytes, at least in part, by using the pre-existing, IL-2–dependent signaling pathways. The Journal of Immunology, 2013, 191:000–000.

A

nplastic lymphoma kinase (ALK) is expressed physiologically only in certain immature neuronal cells (1). However, aberrant expression of ALK has been identified in a number of histologically diverse malignancies, including T and B cell lymphomas, inflammatory myofibroblastic tumors, neuroblastomas, and carcinomas of lung and other organs (1–3). T cell lymphomas (TCLs) that express ALK are recognized as a distinct category of lymphoma. Ectopic expression of ALK in the affected CD4+ T lymphocytes is the result of chromosomal translocations involving the ALK gene and several partners; the most frequent, by far, is the nucleophosmin (NPM) gene (3). The NPM/ALK chimeric protein is constitutively expressed and persistently activated through autophosphorylation (4, 5). NPM/ALK displays potent cell-transforming properties, as demonstrated both in vitro (4, 6) and in vivo (7, 8). NPM/ALK mediates its oncogenicity by activating a number of cell-signal pathways, including STAT3 and STAT5, and MEK/ERK (9–11). Chronic activation of these signal transmitters leads to persistent expression of genes, the protein products of which are involved in such key cell functions as promotion of cell proliferation and protection from apoptotic cell death. However, the fundamental question of how ALK, the tyrosine kinase physiologically expressed exclusively by the neural cells, is able to transform nonneural cells, such as CD4+ T lymphocytes, remains unanswered.

IL-2 and functionally related cytokines signal through receptors that share the common γ (IL-2Rγ) chain (12, 13) and are critical for maturation, proliferation, and survival of the normal CD4+ T lymphocytes and other immune cells (14–17). Analysis of the intracellular signaling pathways indicates that many of these IL-2–regulated cell functions are primarily mediated by the MEK-ERK, PI3K-Akt, and STAT5 pathways (18–27).

In this study, we report that NPM/ALK-induced cell signaling results in a distinct gene expression pattern that closely resembles the gene expression changes induced by IL-2. These findings indicate that NPM/ALK succeeds in transforming the target CD4+ T lymphocytes, at least in part, by mimicking the effects of IL-2, the natural key regulator of these cells.
Materials and Methods

**ALK** and **ALK** ALC cell lines

NPM/ALK-expressing Sadhl-1, J66, Sup-M2, and Karpas 299 cell lines were derived from ALK+ TCL patients (9-11, 28-29). IL-2−dependent TCL cell lines Sez-4 and SeAx were derived from ALK+ TCL patients (30). The cell lines were cultured at 37°C and 5% CO2 in RPMI 1640 medium supplemented with 2 mM L-glutamine, 10% heat-inactivated FBS, 1% penicillin/streptomycin mixture and, where applicable, 200 U IL-2 (Bender MedSystems).

Microarray analysis

The ALK+ TCL Sudhl-1 cell line was treated in triplicates with the ALK inhibitor, CEP-14083, or the compound’s solvent for 6 h. The Sez-4 cell line was starved of IL-2 for 16 h and placed into six-well plates in 10 ml RPMI 1640/10% FBS for 2 h, followed by the addition of IL-2 (200 U) or medium alone for 4 h. The isolated RNA was reverse transcribed, bixin labeled, and hybridized to the U133 Plus 2.0 array chips (Affymetrix), as described (30). Microarray data were normalized using the MAS5 algorithm and analyzed using Partek GS (Partek). Differentially expressed genes were identified using ANOVA. A gene list with a 5% false discovery rate (FDR = 0.05) was used to identify the target genes common for both NPM/ALK and IL-2. Hierarchical clustering was performed by Cluster 3.0 and presented using Java Tree View 1.1.0. The Ingenuity and Gene Ontology databases were used for functional analysis of gene lists.

**Western blot and Abs**

The cells were washed, centrifuged, and lysed in lysis buffer supplemented with 0.5 mM PMSF, phosphatase inhibitor cocktails I and II (Sigma), and protease inhibitor (Roche), according to the manufacturer’s specifications. For normalization of gel loading, the protein extracts were assayed by the Lowry method (Bio-Rad Dc protein assay). Typically, 10–50 µg of protein was loaded per lane. To detect total proteins, we used anti-Egr-1 Ab (Cell Signaling) and anti–Fosl-1, anti–Socs3, anti–Irf-4, and anti-actin Abs (all from Santa Cruz). To examine protein phosphorylation, the membranes were incubated with the Abs specific for STAT3 Y705, STAT5 Y694, and Erk1/2 T202/Y204 (all from Cell Signaling). The membranes were incubated with the appropriate secondary peroxidase-conjugatedAbs. The blots were developed using the ECL Plus Western blotting detection system (Amersham).

**Flow cytometry**

Cells (0.5 × 10^6) were washed in 1× PBS and stained for 20 min with mouse Ab against CD25 (dilution 1:10; FITC; BD Pharmingen) or FITC-labeled mouse IgG1 isotype controls. After double washing in 1× PBS, the stained cells were applied to the flow cytometer (FACSCalibur; Becton Dickinson), and 20,000 events were analyzed. Results from the cell staining were presented as the mean channel fluorescence signal from three experiments.

**Enzyme immunoassay**

To detect the secreted, soluble form of CD25 (sCD25), we used a commercially available sCD25 (soluble IL-2Rα) human ELISA kit (Quantikine, DR2A00; R&D Systems), according to the manufacturer’s instructions. Briefly, samples were diluted 10-fold and incubated in duplicates (50 µl/well) to the microplate that was precoated with CD25 Ab, and incubated for 3 h with 100 µl a second CD25 Ab-peroxidase conjugate. After washing, substrate solution (200 µl) was added for 20 min, followed by the addition of stop solution (50 µl). OD was measured at 450 nm, using a microplate reader (Titertek Multiskan). Standards of known sCD25 concentrations were analyzed and used as reference.

**Kinase inhibitors**

A potent ALK inhibitor (CEP-14083) and its structurally related ALK noninhibitory counterpart (CEP-11988), both used at 175 nM, were described previously (28). Pan-Jak (Jak 1; Calbiochem) is a quinolin deriv-ative with the structure 2-(1,1-dimethylethyl)-9-fluoro-3,6-dihydro-7H-benz(α)-imidaz(4,5-f) isquinolin-7-one (30). It inhibits the enzymatic function of all four members of the Jak family, with an IC50 of 15 mM for Jak1, 1 mM for Jak2, 5 mM for Jak3, and 1 mM for Tyk2 in vitro kinase activity–inhibition assays. The inhibitor preferentially target-ging Jak3 (30) displays an in vitro IC50 kinase activity inhibition at 2 µM for Jak1, 20 µM for Jak2, and 100 µM for Jak3 (Promega, Madison, WI) and PD98059 (Calbiochem, La Jolla, CA) are MEK1/2 inhibitors and were used at concentrations of 15 and 20 µM, respectively (29).

Small interfering RNA assay

A mixture of four (ERK1-, ERK2-, STAT3-, and STAT5a- or STAT5b-specific) small interfering RNA (siRNA) or nonsense siRNA (all from Dharmaco) was introduced into cells at 0.1–10 mM/l by lipofection with Lipofectamine (DMRIE-C; Invitrogen). For the Sez-4 cell line, cells were harvested after 48–96 h of culture in the medium containing IL-2.

**Cell-proliferation assay**

Forty-eight hours after the knockdown of Egr-1, cell proliferation was evaluated by detection of BrdU incorporation using the commercially available kit cell for ELISA (Roche), according to the manufacturer’s protocol. In brief, cells were seeded into 96-well plates (Corning), at a concentration of 5 × 10^3 cells/well, in RPMI 1640 medium supplemented with 10% FBS and labeled with BrdU (Roche) for 4 h. After centrifugation (10 min at 300 × g), supernatant removal, and plate drying, the cells were fixed, and DNA was denatured by the addition of 200 ml FixDenat reagent. The amount of incorporated BrdU was determined by incubation with a specific Ab conjugated with peroxidase, followed by colorimetric conversion of the substrate and absorbance evaluation in the ELISA plate reader.

**Results**

**Gene expression profile is similar in IL-2-stimulated ALK+ TCL and ALK+ TCL cells**

Previous studies indicated that several key signal-transduction pathways, including Jak-STAT, MEK-ERK, and mTORC1, are aberrantly activated in both IL-2−dependent ALK+ TCL and ALK+ TCL cells (9–11, 28–30). To further explore the apparent similarity, we analyzed these and additional pathways by com-
paring genome-wide gene expression patterns in ALK− TCL cells in response to IL-2 and in ALK+ TCL cells in response to ALK inhibition. By applying a ≥1.5-fold change in gene expression and an FDR = 0.05 as filter thresholds, we identified 3305 genes modulated by IL-2 in the ALK− TCL–derived Sez-4 cells and 4319 genes affected by ALK inhibition in the ALK+ TCL Sudhl-1 cells (Fig. 1A). Among these two sets of gene transcripts, 1302 were shared and accounted for 39 and 30% of all modulated genes in the Sez-4 and Sudhl-1 cells, respectively. When no fold threshold and an FDR < 0.05 were applied, we found that the expression of 13,412 and 9,735 genes was changed in the Sez-4 and Sudhl-1 cells, respectively. Strikingly, 5909 of these genes were regulated simultaneously in both cell types, representing 44 and 67% of all modulated genes in the Sez-4 and Sudhl-1 cells, respectively (Fig. 1B). Not surprisingly, given the emerging similarity between IL-2–induced and NPM/ALK signaling, almost all of the jointly regulated genes were modulated in the opposite direction in response to IL-2 stimulation and ALK inhibition. Fig. 2 depicts the set of 155 common genes for which the expression was the most affected by the cell modulation (≥2-fold change in expression; FDR 0.05). For some of the genes, up to four probes were present in the array and, as can be seen, they tend to cluster together, indicating the high technical quality of the data.

**IL-2 and NPM/ALK activate an overlapping spectrum of signaling pathways**

By analyzing the genes regulated in common using the Gene Ontology and Kyoto Encyclopedia of Genes and Genomes databases, we assigned these genes to cell-signaling pathways (Table I). When sorted according to the highest probability (the lowest p value), two signaling pathways—Jak/STAT and IL-2—topped the list. Although reassuring, activation of IL-2 signaling in Sez-4 cells was totally predictable given that IL-2 was used as the stimulus in these cells. However, the similar designation of the gene expression reprogramming induced by NPM/ALK further indicated that this oncogenic kinase activates the same signaling pathways as does IL-2. Interestingly, another top jointly regulated pathway was circadian rhythm signaling, which was reported to be involved in the pathogenesis of leukemias and lymphomas (31). Finally, identification of p53 signaling as another highly regulated pathway is in agreement with the reported ability of NPM/ALK to inhibit p53 via MDM2 and JNK (32).

**IL-2– and NPM/ALK-modulated genes are translated into proteins**

To affirm the biological relevance of the genomic analysis, we examined the expression of five selected genes regulated by both IL-2 and ALK on the protein level: CD25 (IL-2Rα), Egr-1, Fosl-1, SOCS3, and Irf-4. These genes were selected based on either their known functional importance or novelty, at least in the context of IL-2 and ALK signaling. By using flow cytometry to detect CD25 and Western blotting to detect the other remaining genes, we identified the expression of all five proteins in Sez-4 and Sudhl-1 cells, as well as in another IL-2–dependent ALK− TCL cell line (SeAx) and three additional ALK+ TCL cell lines listed in Fig. 3.

**IL-2 and NPM/ALK induce CD25 expression through STAT5 and STAT3**

To confirm the roles of IL-2 and ALK in inducing expression of CD25, we exposed Sez-4 cells to IL-2 and Sudhl-1 cells to ALK inhibitor. Indeed, IL-2 stimulation markedly enhanced and ALK inhibition greatly diminished expression of CD25 (Fig. 4A). To identify cell-signaling pathways involved in induction of CD25 expression downstream of IL-2R and NPM/ALK, we applied an inhibitor against the Jak family with the highest activity against Jak3, as well as two inhibitors of MEK, all used at the pretested effective doses (Fig. 4A). Although the Jak inhibitor profoundly diminished CD25 expression in the IL-2–treated Sez-4 cells in accordance with the key role of Jak3 in IL-2 signaling (28), it had no effect on CD25 expression in Sudhl-1 cells, confirming our previous finding that NPM-ALK signaling is Jak3 independent (29). Inhibition of MEK by two different inhibitors did not affect CD25 expression in either Sez-4 or Sudhl-1 cells, indicating that
the MEK-ERK pathway is not involved in the regulation of CD25 expression.

Because STATs, in particular STAT5, have been implicated in the induction of CD25 (33, 34), we next examined whether their siRNA-induced depletion affects CD25 expression in Sez-4 and Sudhl-1 cells. Indeed, depletion of STAT5a and STAT5b (Supplemental Fig. 1, upper panel), markedly diminished CD25 expression in Sez-4 cells, examined at both the cell surface level (Fig. 4B, left panel, Supplemental Fig. 2, left panels) and the soluble (sCD25) level (Fig. 4B, right panel). In agreement with the MEK-inhibition data (Fig. 4A), depletion of ERK1 and ERK2 had no effect on CD25 expression. Although ALK+ TCL cells, including Sudhl-1 cells, typically fail to express STAT5a because of epigenetic silencing of its gene (35), they weakly express STAT5b (35, 36) and very strongly express STAT3 (9, 28). Although depletion of STAT5b in Sudhl-1 cells (Supplemental Fig. 1, lower panel) did not significantly affect CD25, depletion of STAT3 had a profound inhibitory effect on CD25 expression (Fig. 4C, Supplemental Fig. 2, right panels). As in Sez-4 cells, depletion of ERK1 and ERK2 exerted no significant effect on CD25. These data indicate that the STAT family members, but not the MEK-ERK pathway, induce CD25 expression in both ALK+ TCL and ALK+ TCL. Although STAT5 plays a key role in the former cell type, STAT3 is critical for CD25 expression in the latter cell type.

**STAT and MEK-ERK pathways play a similar role in modulation of specific genes in both ALK− and ALK+ TCL**

To identify the pathways triggering expression of the other selected genes—Egr-1, Fosl-1, SOCS3, and Irf-4—we also used small molecule inhibitors and siRNA technology. Exposure of IL-2–stimulated Sez-4 cells to the Jak inhibitor preferentially active against Jak3 profoundly suppressed expression of all four of the gene protein products, with inhibition of STAT5, STAT3, and ERK phosphorylation serving as positive controls (Fig. 5A, left panel). In addition, expression of Egr-1 and Fosl-1, but not SOCS3 or Irf-4, was inhibited by both MEK inhibitors. Exposure of the NPM/ALK-expressing Sudhl-1 cells to the ALK inhibitor, but not the Jak inhibitor, profoundly suppressed expression of all four proteins, as well as phosphorylation of STAT3, STAT5, and ERK (Fig. 5A, right panel). Similar to Sez-4 cells, expression of both Egr-1 and Fosl-1, but not SOCS3 or Irf-4, was suppressed by the MEK inhibitors. siRNA-mediated depletion of ERK1 and ERK2 in Sez-4 and Sudhl-1 cells also adversely affected expression of Egr-1 and Fosl-1 but not SOCS3 or Irf-4 (Fig. 5B). In contrast, depletion of STAT3 suppressed expression of SOCS3 and Irf-4, but not Egr-1 or Fosl-1, in Sez-4 and Sudhl-1 cells. These data indicate that expression of Egr-1 and Fosl-1 is regulated by the MEK-ERK pathway, whereas expression of SOCS3 and Irf-4 is regulated by the STAT pathway. Furthermore, expression of these selected and representative genes is IL-2 and NPM/ALK dependent.

**Egr-1 plays a role in growth of ALK− and ALK+ TCL cells**

Egr-1 is one of the most strongly regulated genes in both ALK− and ALK+ TCL cells, with upregulation of up to 25-fold in response to IL-2 and downregulation of up to 28-fold in response to ALK inhibition (Fig. 2, data not shown). Egr-1 has been implicated in the carcinogenesis (37), as well as the biology, of normal T lymphocytes (38). However, its role in malignant T lymphocytes remains undefined. To explore Egr-1 function in lymphoma cells, we depleted Egr-1 in Sez-4 and Sudhl-1 cells (Fig. 5C) and evaluated its impact on their proliferative rate. As can be seen in Fig. 5D, Egr-1 loss decreased the proliferation of both cell types to a similar degree, indicating that this transcription factor contributes to the cell growth–promoting properties of both IL-2 and NPM/ALK.

**Discussion**

Although the oncogenic properties of aberrantly expressed and activated ALK, in particular its NPM/ALK variant, are well recognized (1–3), the question of how this kinase, normally expressed solely in neural cells, succeeds in transforming CD4+ T lymphocytes and other nonneural target cells remains only partially answered.

Previous studies indicated that NPM/ALK mediates its oncogenicity by activating a number of cell-signaling pathways, including STAT3, STAT5, MEK/ERK, PI3K/Akt, and mTORC1 (9–11). In retrospect, these signaling pathways are also activated by...
IL-2 (18–27). Through a series of focused experiments using ALK+ TCL and IL-2–dependent ALK+ TCL cells, we now provide direct evidence that NPM/ALK activity closely resembles the effects of IL-2 stimulation. The Sudhl-1 cell line was cultured for 8 h in the presence of an ALK inhibitor, a nonactive formulation of the ALK inhibitor (negative control), or Jak/STAT and MAPK inhibitors. 

It is interesting, in this context, that ALK+ TCL cells display loss of the common γ (IL-2Rγ) chain (39), the key component of the cell surface receptor complex activated by IL-2 and functionally similar cytokines. This loss of IL-2Rγ expression is due to epigenetic silencing of the IL-2Rγ gene induced by NPM/ALK itself (39). Together with our current observation of NPM/ALK-mediated cell signaling recapitulating IL-2 function, this finding indicates that NPM/ALK transforms the target CD4+ T cells by rendering them independent of external stimuli provided by IL-2–type cytokines on one hand and by constitutively activating intracellular signaling pathways normally regulated by these cyto-

**FIGURE 4.** Involvement of STAT and MEK-ERK pathways in regulation of CD25 expression. (A) The IL-2–dependent Sez-4 cell line was starved of IL-2 for 16 h and stimulated by medium alone or IL-2 for 12 h. Inhibitors of Jak and MEK (U0126 and PD98059) were added to the culture media 1 h before the IL-2 stimulation. The Sudhl-1 cell line was cultured for 8 h in the presence of an ALK inhibitor, a nonactive formulation of the ALK inhibitor (negative control), or Jak/STAT and MAPK inhibitors. (B and C) Alternatively, siRNA induced specific depletion of the listed targets in both cell types, with nonsense siRNA serving as control. Surface expression of CD25 was visualized by specific staining with FITC-labeled Ab against CD25 and analyzed by flow cytometry (left panels). The concentration of sCD25 was determined by EIA (right panels). The depicted flow cytometry experiments are representative of three independent experiments (n = 3). EIA to detect sCD25 was performed twice (n = 2), each time the samples were analyzed in duplicates (n = 2).
kines on the other hand. These combined features may explain, to a large degree, the remarkable potency of NPM/ALK as an oncogene (1–4, 6–8).

Although strikingly similar, the activities of NPM/ALK and IL-2 in ALK+ TCL and ALK– TRL, respectively, do not seem to be identical. STAT3 plays the critical role in NPM/ALK-induced oncogenesis, whereas STAT5 signaling seems to be more important in IL-2 signaling, including the IL-2–dependent ALK+ TRL cells. Of note, the STAT5a gene is epigenetically silenced in ALK+ TRL (35). Our data demonstrating that STAT5 and STAT3 play a key role in inducing CD25 expression in IL-2–stimulated Sez-4 cells (Fig. 4B) and in NPM/ALK-transformed Sudhl-1 cells (Fig. 4C), respectively, indicate that, at least in some instances, STATs may substitute for each other, possibly depending on their relative concentration and activation status, and in part compensate for loss of STAT5a expression. Furthermore, a previous study found similarities between signaling induced by NPM/ALK and the TCR (40), most notably that both activated the NFAT transcription factor. This finding indicates that, in addition to IL-2–type signaling, NPM/ALK mimics some aspects of signaling from another receptor complex that is critical for the function of normal CD4+ T lymphocytes. Similar to IL-2Rγ, ALK+ TRL cells display NPM/ALK-dependent epigenetic gene silencing and, hence, loss of expression of several members of the TCR complex, including the TCR itself, its partner CD3, and the key downstream kinase ZAP-70 (41). This observation suggests that NPM/ALK inhibits in the transformed CD4+ T lymphocytes also the stimuli generated by the TCR complex, in addition to inhibiting cell signals normally provided by IL-2–type cytokines.

Egr-1 was among the genes regulated in common by NPM/ALK and IL-2 that attracted our attention. This transcription factor can be induced in diverse tissues by a spectrum of growth factors.
stress stimuli (37, 38). Interestingly, Egr-1 has been implicated in both the promotion and inhibition of carcinogenesis, indicating that its activity is complex and dependent on the cellular and signaling context. Accordingly, Egr-1 is shown to induce proliferation of prostatic carcinoma cells (37). However, in colorectal carcinoma cells exposed to Cox inhibitors, Egr-1 expression promotes cell apoptosis (42). With regard to normal T lymphocytes, Egr-1 is induced in response to TCR signaling, and it promotes synthesis of cytokines, including IL-2 and TNF-α (38). Our findings that Egr-1 expression can be induced by IL-2, as well as by NPM/ALK, are novel and have potential basic and translational implications. Although the role of such induction in normal T lymphocytes needs to be established, our observation that Egr-1 contributed to the growth of malignant T cells from both ALK+ and ALK− TCL (Fig. 5D) suggests that it may become a therapeutic target in these, and possibly other, types of TCL.

There is accumulating evidence that IL-2–type signaling may play a key role in the pathogenesis of ALK+ TCL, as well as other types of TCL. These lymphomas include cutaneous TCL (22, 43) and adult-type TCL/lymphoma (44), in which aberrant activation of the IL-2–dependent pathways, in particular the Jak/STAT signaling has potentially important translational implications, with cytokines from the IL-2 family in the maturation and functional dysregulation of IL-2–type signaling. In retrospect, this emerging evidence further expanding the list of lymphomas with Jak3-activating mutations within the pseudokinase domain was provided by 36 patients with adult-type TCL/lymphoma (45), providing additional evidence that this kinase, and, thus, IL-2–dependent signaling, promotes lymphomagenesis. More recently, another set of Jak3-activating mutations within the pseudokinase domain was found in tumor tissues from 23 of 65 patients with NK/T cell lymphoma (46), further expanding the list of lymphomas with dysregulation of IL-2–type signaling. In retrospect, this emerging reliance on IL-2 signaling by the various types of T cell malignancies may not be that surprising, given the critical role of cytokines from the IL-2 family in the maturation and functional differentiation of normal T lymphocytes. This dependence on IL-2 signaling has potentially important translational implications, with the key kinases in the pathway representing attractive therapeutic targets. Although NPM/ALK itself can be targeted effectively by small molecule inhibitors in ALK+ TCL, with the preliminary clinical evidence being very encouraging (47), Jak1 and Jak3, the kinases transmitting the stimuli generated by IL-2 and similar cytokines, should be equally attractive targets in the other types of lymphoma. This may be particularly true for the lymphomas that carry activating mutation of Jak3 (45, 46).

Disclosures

The authors have no financial conflicts of interest.

References


